REMARKS

The claims have been amended to overcome the rejection under 35 U.S.C. § 112 set forth on page 4 of the Office action. The suggestion made by the Examiner to change "characterized by" to "has" has been adopted.

New claims have been added which, applicants believe, do not raise new issues or require additional searching. A review of the added claims will reveal that the limitations of claims 2, 3, 5 and 8 have simply been added to the independent claims pending in the application. Thus, these claims simply specify the types of tumor used in the model.

No new matter has been added by these amendments and entry of the amendments is respectfully requested.

The Invention

The invention is directed to an exceptionally faithful animal model for the progression of human neoplastic disease. The model uses immunodeficient subjects, including mice, rats, and any other mammalian subject that may be made immunodeficient and requires two specific features. First, the tumor to be evaluated must be inserted orthotopically - *i.e.*, in the same tissue in which it is found in humans. Second, it must be introduced as a histologically intact tissue, not as a cell suspension. This combination results in a faithful reproduction of the human disease, *including the metastatic features thereof.* This is the result of the combination of the orthotopic nature of the implantation and the preservation of the architecture by using an intact segment of the tissue. The art cited herein does not, in applicants' view, suggest this combination of features. In particular, it is apparent as will be discussed below that the art cited while perhaps providing a model reflective of the primary tumor, is not at all reflective of the progression of the disease *per se*, since no metastases are observed in any of the documents cited. It is well known that colon and lung cancer are highly metastatic. Thus, clearly orthotopic implantation of cell suspensions does not provide an adequate model of the disease. Nor does transplantation of human renal cell carcinoma into a non-orthotopic location reflect correctly the

disease progression. It is only by combining orthotopic implantation with implantation of an intact sample that a successful model is achieved.

Formal Matters

Applicants note the requirement that applicants offer to surrender the original patent in the event the claims herein are found allowable. Applicants hereby offer to do so upon indication of allowance of the claims herein.

Applicants note with appreciation the acceptance of applicants petition to accept the declaration and power of attorney signed by the sole assignee of interest.

The Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 19, 26 and 29 not limited to rodents, but directed to any immunodeficient nonhuman mammal as the recipient model, were rejected as lacking enablement in the specification. Respectfully, it is believed that the application supports claims of this scope. Methods for making mammals, in general, immunodeficient are well known in the art and include treatment with compounds such as cyclosporin, and irradiation. As to the sufficiency of such immunodeficiency, this requirement is inherent in the model itself. If the transplant is rejected, there is insufficient immunodeficiency obtained and additional treatment with radiation or immunosuppressant compounds would be required. It is well within ordinary skill to optimize these parameters.

Thus, although rodents are clearly the most convenient types of mammalian subjects for the models of the invention, the preparation of other immunodeficient mammals, should one desire to do so, is within ordinary skill.

The Rejections Under 35 U.S.C. § 112, Second Paragraph

This basis for rejection has been mooted by amendment.

The Rejections Under 35 U.S.C. § 103

There appears to be some confusion about the claims pending in the present application. According to applicants' records, this application, which is a reissue of U.S. patent 5,569,812, was filed with the 12 claims as issued, and additional claims to a total of 29 claims. Various of the rejections refer to claims with higher numbers. This may have resulted from reference to a formerly copending application for reissue of U.S. patent 5,491,284. This reissue application has since been abandoned as redundant with the application herein. Nevertheless, the substance of the rejections is understood and response is made as follows.

First, all of the rejections depend on McLemore, *et al.*, and/or Wang, *et al.*, as primary references in combination with Otto, *et al.* The additional documents cited, Giovanella and Reddy, *et al.*, are cited for specific features upon which applicants do not rely for patentability. Giovanella is cited as suggesting the use of rats rather than mice, and Reddy is cited as showing tumor models in SCID mice. It is assumed that these documents in combination with the documents used a primary and secondary references are applied to claims specifically directed to rats and SCID mice. These claims are patentable over the art for the same reasons that the remaining claims are thus patentable. Thus, all of the rejections under 35 U.S.C. § 103 may be discussed together; the claimed invention is patentable whether or not limited to SCID mice or rats.

The primary documents cited, Wang and McLemore report purported tumor models in nude mice where suspensions of tumor cells are implanted in the organs from which the tumor cells were originally derived. (Wang is actually clear that a cell suspension is used since tumor cell lines were used as a control and Wang refers to tumors being initiated "from a small number of injected cells" on page 331). The Wang document relates to colorectal tumor cells and the McLemore document relates to lung tumor cells. While it is correct that there is some indication in these documents that the primary growth of the tumor is mimicked in these models, it is clear that the overall course of the disease is not since no metastases are observed. Wang reports on

page 331 only that "colonic tumors invaded the various subregions of the colonic wall and mimic the original pattern characteristic of patient tumors" the word "original" may be significant here. There was some observation of tumor cells to grow within lymphatics and to a lesser degree within veins. There is no indication that metastases to various other locations is observed as would have been the case had the disease been properly mimicked.

McLemore is even more explicit that, contrary to observations of the progress of human lung cancer, the injected lung cancer cells remain confined to the lungs in the model. On page 5136 it is noted that 91% of the tumors implanted were localized to the right lung and other tumor locations included smaller percentages in the left lung, trachea or paratracheal area. It is noted that the Office calls attention to Table 1 on page 5133 as referring to metastatic tumors; however, it appears that this refers to the nature of the tumor cells implanted rather than the locations from which they are recovered. This explanation is set forth at page 5137, left-hand column. There is thus no observation of any distant metastases as would have been expected from lung tumors had the disease followed the course it follows in humans. Thus, neither Wang nor McLemore provide an incentive to utilize orthotopic transplantation generally as an accurate model for human tumor progression. Indeed, Wang does not appear particularly enthusiastic about the orthotopic model generally and McLemore concludes only that organ-specific *in vivo* implantation of tumors facilitates optimal tumor growth. Nothing is concluded about providing a faithful model of the progress of the disease.

Otto, *et al.*, is cited as showing the transplantation of tumor tissue as opposed to cell suspensions in order to study the effects of irradiation on tumors. There is no suggestion in Otto to utilize such implantation (which is not orthotopic) as a model for the progress of the disease. The object of Otto is simply to test the effect of irradiation on tumor acceptance and tumor growth. Otto is not even attacking the same problem as that addressed by applicants. In addition, there is no evidence set forth in Otto that any metastases occur as a result of this implantation.

One of the advantages of the present invention is the ability of the surgically orthotopically implanted tissue to mimic the course of human disease by metastasizing through the subject. This does not occur in any of the cited documents. The reminder provided by Office that patentability of product by process claims is based on the product itself is acknowledged; however, there is no rejection based on anticipation, and, as stated above, the product itself is quite different in that metastasis occurs in the model systems claimed herein, but does not occur in the animals described in the cited documents.

It is also clear that there is no motivation to combine the teachings of the primary references with those of Otto.

The Federal Circuit has recognized three valid criteria on which the Office may base an assertion of motivation to combine documents in *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998). None are met here. The first of these criteria is that the suggestion to combine is found in the documents themselves. The Office has not pointed to any discussion in Wang or McLemore which would point the skilled artisan to Otto, or any suggestion in Otto that would point the skilled artisan to the primary references. The second criterion is the nature of the problem to be solved. The nature of the problem to be solved in Otto is clearly different from the nature of the problem to be solved in Wang and McLemore. Wang and McLemore purport to describe models for the primary progression of human tumors (though not metastases); the problem to be solved in Otto is simply to test the effect of irradiation on tumor growth and none of the cited documents purports to solve the problem addressed by the applicants - *i.e.*, to provide a model for the total progress of the disease including metastases. The third criterion is that one of the documents is of such prominence that all persons of ordinary skill would be aware of it - such as the Kohler and Milstein description of monoclonal antibodies. Clearly none of the documents cited here fulfill this criterion.

Since none of the criteria for asserting motivation to combine are present, it is respectfully submitted that such combination relies on the invention itself for guidance, a reliance which as applicants are certain the Office is aware, is not permissible.

The only motivation cited by the Office is based on the asserted "benefits" of using tissue over cell suspension; however, "benefits" as seen by Otto, *et al.*, if any, relate only to the problem to be solved by Otto, not to the problem to be solved by Wang or McLemore. And as pointed out above, none of the documents actually shows metastasis of the tumors implanted, as would be required in an accurate model.

For these reasons, it is believed that the rejection under 35 U.S.C. § 103 may properly be withdrawn.

CONCLUSION

Preparation of non-rodent immunodeficient mammals is within ordinary skill of the art, and thus rejection of certain claims under 35 U.S.C. § 112 may be withdrawn. As demonstrated above, the methods and compositions of the invention are not suggested by the cited art. Thus, it is respectfully requested that claims 1-65 be passed to issue forthwith.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 312762001530. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

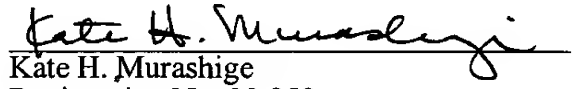
Dated: April 4, 2001 By: 

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EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A nude rodent model for human neoplastic disease, wherein said rodent [is characterized by:

having] has histologically intact human neoplastic tissue of at least 1 mm^3 in size transplanted onto an organ of said rodent which corresponds to the human organ from which said tissue is originally obtained; and

[having] has sufficient immuno-deficiency to allow said transplanted neoplastic tissue to grow and mimic the progression of the neoplastic disease in the human donor.

13. (Amended) A nude rodent model for human neoplastic disease, wherein said rodent [is characterized by:

having] has histologically intact human neoplastic tissue of at least 1 mm^3 in size transplanted onto an organ of said rodent which corresponds to the human organ from which said tissue is originally obtained; and

[having] has sufficient immuno-deficiency to allow said transplanted neoplastic tissue to grow and mimic the progression of the neoplastic disease in the human donor.

15. (Amended) An immunodeficient rodent model for human neoplastic disease, wherein said rodent [is characterized by:

having] has histologically intact human neoplastic tissue of at least 1 mm^3 in size transplanted onto an organ of said rodent which corresponds to the human organ from which said tissue is originally obtained; and

[having] has sufficient immuno-deficiency to allow said transplanted neoplastic tissue to grow and mimic the progression of the neoplastic disease in the human donor.

19. An immunodeficient non-human mammal model for human neoplastic disease, wherein said non-human mammal model [is characterized by:

having] has histologically intact human neoplastic tissue of at least 1 mm^3 in size transplanted onto an organ of said non-human mammal which corresponds to the human organ from which said tissue is originally obtained; and

[having] has sufficient immuno-deficiency to allow said transplanted neoplastic tissue to grow and mimic the progression of the neoplastic disease in the human donor.

27. (Amended) A nude rodent model for human neoplastic disease, wherein said rodent [is characterized by:

having] has histologically intact human neoplastic tissue transplanted onto an organ of said rodent which corresponds to the human organ from which said tissue is originally obtained; and

[having] has sufficient immuno-deficiency to allow said transplanted neoplastic tissue to grow and mimic the progression of the neoplastic disease in the human donor.

28. (Amended) An immunodeficient rodent model for human neoplastic disease, wherein said rodent [is characterized by:

having] has histologically intact human neoplastic tissue transplanted onto an organ of said rodent which corresponds to the human organ from which said tissue is originally obtained; and

[having] has sufficient immuno-deficiency to allow said transplanted neoplastic tissue to grow and mimic the progression of the neoplastic disease in the human donor.

29. (Amended) An immunodeficient non-human mammal model for human neoplastic disease, wherein said non-human mammal model [is characterized by:

having] has histologically intact human neoplastic tissue transplanted onto an organ of said non-human mammal which corresponds to the human organ from which said tissue is originally obtained; and

[having] has sufficient immuno-deficiency to allow said transplanted neoplastic tissue to grow and mimic the progression of the neoplastic disease in the human donor.